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REMARKS

The present invention relates generally to providing fluorescent particles useful in determining analyte concentrations in aqueous solutions. The particles of the present invention incorporate dye pairs that are selected to provide advantageously large Stokes shifts (i.e., the shift in wavelength between peak light absorption and peak fluorescent emission) through resonant energy transfer between the members of the dye pairs. *See, e.g.*, specification, page 13, lines 5-23. In addition, the fluorescent particles of the present invention can provide reduced quenching of the fluorescent signal. *See, e.g.*, specification, page 14, lines 12-18.

Claims 30-46 are presently pending in the application, with claims 32-44 and 46 presently under consideration by the Examiner, and claims 45-46 removed from consideration by restriction requirement.

Applicants respectfully request reconsideration of the claims in view of the following remarks.

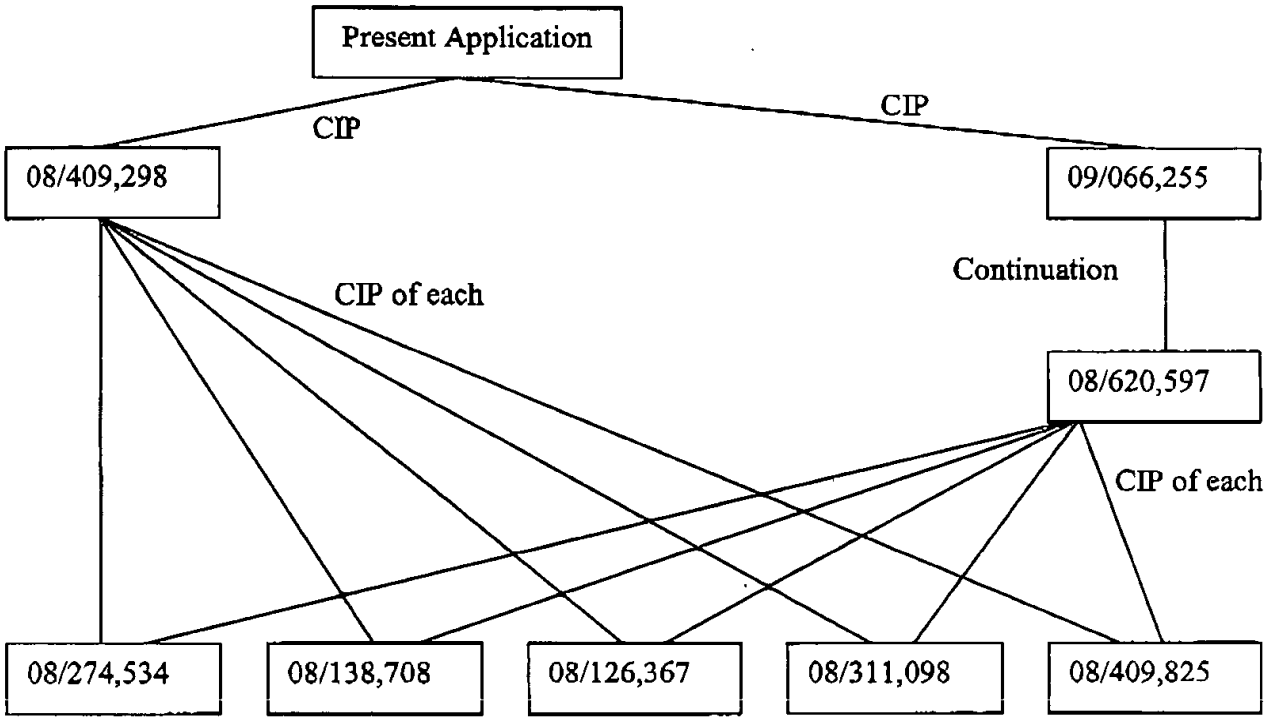
Non Art-Related Remarks

Personal Interview

Applicants acknowledge with thanks the courtesy shown to Applicants' representative in the personal interview held on April 22, 2003. The following remarks reflect the discussions held during the interview.

Priority Claim

Applicants respectfully submit that the Examiner has misunderstood the rather complicated priority claim in the present application. Applicants do not assert that the present application is a continuation of parent application 08/620,597 as the Examiner believes. *See, e.g.*, Paper No. 9, page 3, last paragraph. In an effort to assist the Examiner, the following drawing is provided to clearly show the relationships between the present application and the various priority documents.



Oath/Declaration

Applicants respectfully submit that the Examiner's objection to the oath/declaration filed in the present application is in error, and is based on the misunderstanding of the priority claim discussed above. Because the necessary copendency for benefit of each parent application was present at the time the present application was filed, Applicants request that the objection be withdrawn.

Restriction/Election

Applicants first note that the statement of claims pending in the elected group in the Office Action on page 4, paragraph 4, contains a typographical error; the elected group encompasses claims 30-42 and 45-46.

In addition, Applicants maintain the objection to the Examiner's restriction of claims 43 and 44 from consideration. As discussed during the personal interview, any complete search for independent claim 30 *necessarily* must include a search for dependent claims 43 and 44, which

depend from and further limit claim 30. Applicants note that, because claim 30 is written using open "comprising" language, any prior art embodiment within the scope of dependent claims 43 or 44 is a species of the genus described in claim 30. Therefore, if the Examiner is indicating that such matter will not be searched with regard to claim 30, Applicants respectfully submit that such a search will not be a "thorough search of the prior art" as required by MPEP § 904.02.

Because the search for claim 30 must include a search for dependent claims 43 and 44, no serious burden is presented on the Examiner if all claims are searched and examined. *See*, MPEP § 803 (restriction is only proper when search and examination of the claims presents a serious burden to the examiner).

In accordance with MPEP § 818.03(c), traversal by Applicants preserves the right to later petition the Commissioner to review the restriction. Applicants note that, in the personal interview, the Examiner indicated that the withdrawn claims would be reconsidered in accordance with MPEP § 809.02 should generic claim 30 be found to be allowable.

Art-Related Remarks

Information Disclosure Statement

The Examiner indicates that only references cited by the Examiner have been considered in the present application. Appellants respectfully submit that, in accordance with MPEP § 609(I)(2), the office is obliged to consider any information considered in the parents to the present application, and that such information need not be submitted in the present application for that consideration.

35 U.S.C. § 102

Applicants respectfully traverse the rejection of claims 30-31 and 45 as allegedly being anticipated under 35 U.S.C. § 102(e) by Buechler *et al.*, U.S. Patent No. 6,238,931. The cited patent issued on U.S. Patent Application No. 08/274,534, which, as noted in the foregoing drawing, is a parent of the present application. In addition, because the present application and the cited patent list the same inventive entity, the cited patent is not "an application for patent by another" within the meaning of 35 U.S.C. § 102(e). Thus, U.S. Patent No. 6,238,931 is not

citable as prior art to the present application. Applicants therefore respectfully request that the rejection be reconsidered and withdrawn.

35 U.S.C. § 103

Applicants also respectfully traverse the rejection of claim 30 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Sounik *et al.*, EP 0391284, and Wheeler *et al., J. Am. Chem. Soc.* 106: 7404-10 (1984). Applicants submit that the Examiner has not established a motivation to combine the publications as suggested by the Examiner. Moreover, even if combined as suggested, the publications do not teach or suggest each and every element of the present claims. Thus, no *prima facie* case of obviousness has been established.

To establish a *prima facie* case of obviousness, three criteria must be met; there must be some motivation or suggestion, either in the cited publications or in knowledge available to one skilled in the art, to modify or combine the cited publications; there must be a reasonable expectation of success in combining the publications to achieve the claimed invention; and the publications must teach or suggest all of the claim limitations. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2142. In analyzing obviousness, the Court of Appeals for the Federal Circuit has repeatedly cautioned that:

> [t]he factual inquiry... must be based upon objective evidence of record.... [T]he best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references.... [P]articular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

In re Sang-Su Lee, 277 F.3d 1338, 1343 (internal citations omitted).

The instant claims

In the present case, the instant claims refer to a fluorescent particle that contains certain specific components. In particular, the particle must contain both:

a. a first compound selected from the group consisting of silicon phthalocyanine bis(dimethylhexylvinylsilyloxide) and silicon phthalocyanine bis(trihexylsilyloxide); and

b. a second compound that is a bis(dimethylhexylvinylsilyloxide)-substituted or bis(trihexylsilyloxide)-substituted phthalocyanine, naphthalocyanine, or anthranylocyanine derivative, or a bis(dimethylhexylvinylsilyloxide)-substituted or bis(trihexylsilyloxide)-substituted hybrid phthalocyanine derivative.

The Examiner acknowledges that the primary Sounik *et al.* publication, which allegedly discloses a "mixture of tetrazaporphin dyes which exhibits light absorption over a spectrum range of about 660-850 nm" (*see, e.g.*, Sounik *et al.*, claim 1) does not disclose either of components (a) or (b) of the present claims. Paper No. 9, page 11. The Examiner relies on the secondary Wheeler *et al.* publication, which allegedly discloses silicon phthalocyanine bis (trihexylsiloxide) and silicon naphthalocyanine bis (trihexylsiloxide) as individual molecules, and not as components of a single particle, in order to provide the individual components of the instantly claimed invention. *Id.*

In order to arrive at the instant claims, the Examiner cannot simply place one of the individual molecules allegedly disclosed by the Wheeler *et al.* publication into a particle; instead, the Examiner must provide a motivation to place each of the molecules disclosed by the Wheeler *et al.* publication in a single fluorescent particle in order to provide the instantly claimed invention, despite the fact that the Wheeler *et al.* publication is silent as to providing any such combination.

The cited publications, alone or in combination, do not suggest selecting the claimed combination of compounds for use in particles

Appellants respectfully disagree with the Examiner's assertion that "Sounik et al teaches particles that comprise mixtures of substituted and/or substituted phthalocyanine, naphthalocyanine and anthracyanine structures." Paper No. 9, page 11. Nothing in the sections of the Sounik *et al.* publication discloses any particles, fluorescent or otherwise. Thus, even if the

publications are combined as suggested by the Examiner, each and every element of the instant claims is not provided by the cited publications.

Moreover, the Examiner has not established a motivation to combine the publications as suggested. One possible motivation suggested by the Examiner for combining the cited publications is "because the compounds disclosed by Wheeler et al would fall within the genus of compounds that are claimed by Sounik et al." Paper No. 9, page 12. Applicants respectfully submit that the simple fact that a species of compounds is encompassed by a large genus is not dispositive of a motivation to combine or modify references. Furthermore, nothing in either publication indicates that mixtures of two different compounds, each of which comprise two trihexylsiloxide or dimethylhexylvinylsiloxide ligands, should be selected from the large genus disclosed in the Sounik *et al.* publication.

As discussed above, the secondary Wheeler *et al.* publication is silent as to combinations of compounds. As for the primary Sounik *et al.* publication, there is only a broad statement that the possible choice of ligand (Z) would be selected from amongst a halogen, hydroxyl, oxido, siloxy or an aliphatic, acyclic, or aromatic substituent having 1-12 carbon atoms. The Sounik *et al.* publication also states that the molecule may comprise 0, 1, or 2 of these ligands (Z). *See, e.g.*, Sounik *et al.*, page 4, lines 21-22. Thus, from amongst the numerous possible combinations within this genus, one must perform the following steps, without any guidance to do so, in order to arrive at the present claims:

(i) select a molecule comprising an aliphatic ligand (Z),

(ii) modify the aliphatic group to provide a trihexylsiloxide group,

(iii) select two such ligands (Z) on the molecule,

(iv) combine the molecule with a second molecule that is also selected to include each of (i)-(iii), and

(v) provide this combination as a fluorescent particle.

Given that no such combination of molecules is suggested in either publication, as part of a particle or otherwise, fluorescent or otherwise, and given the number of variables that must be

selected in order to modify the primary Sounik *et al.* publication to provide every element of the instant claims, Applicants respectfully submit that the skilled artisan would not be motivated by the alleged fact that "the compounds disclosed by Wheeler et al would fall within the genus of compounds that are claimed by Sounik et al." (Paper No. 9, page 12) to select the necessary components for combination in the manner claimed.

A second possible motivation suggested by the Examiner for combining the cited publications is that the Wheeler *et al.* publication states "[t]he presence of trialkylsiloxy groups on the central Si atom leads to relatively high solubility in these compounds and permits studies of solutions of them at the millimolar level." Paper No. 9, page 12. The Examiner provides no indication, however, as to how this "relatively high solubility" bears in any way on the proposed combination with the primary Sounik *et al.* publication, and thus provides no indication as to why this would motivate the skilled artisan to combine the publications as suggested. Furthermore, the statement that such molecules "permit studies" is an indication that the properties of trialkylsiloxy groups in such molecules are not well established, and may be unpredictable. The exploration of such a general approach that seems to be promising, when the prior art gives only general guidance as to the particular form of the claimed invention, is merely an "obvious to try" rationale that cannot support an obviousness rejection. *See, e.g.*, MPEP §2145(X)(B).

Applicants also disagree that the skilled artisan would allegedly have a reasonable expectation of success in pursuing this general approach "because Wheeler et al further shows states [sic] that the compounds show high thermal and chemical stability and interesting... optical properties." Paper No. 9, page 12. In fact, the Wheeler *et al.* publication shows no such thing. Rather, Applicants respectfully submit that this statement takes out of context the very first line of the Wheeler *et al.* publication, which states in its entirety (emphasis added):

> Phthalocyanine compounds <u>often</u> show high thermal and chemical stability and interesting optical and electrical properties.

This general statement concerning phthalocyanine compounds is equivocal, in that it indicates that not all molecules of this class exhibit such properties. Moreover this general

statement says nothing about the particular molecules disclosed in the Wheeler *et al.* publication, on which the Examiner relies in the obviousness rejection.

There is no suggestion of similar properties in the cited publications

Additionally, there is nothing in either publication cited by the Examiner indicating that the molecules disclosed in the primary Sounik *et al.* publication have similar properties to those disclosed in the secondary Wheeler *et al.* publication. The Examiner contends that the light absorption characteristics of the molecules disclosed by the Wheeler *et al.* publication "[correspond] to the range of absorption requited by Sounik et al." Paper No. 9, page 12. Applicants respectfully submit that this is incorrect. Rather, the Sounik *et al.* publication states on page 2, lines 43-44, that the compositions disclosed therein "[exhibit] light absorption over a spectrum range of about 660-860 nm" (emphasis added). Such light absorption properties are shown, *e.g.*, in Figs. 1 and 2 of the Sounik *et al.* publication, which show absorption over this entire range. In contrast, the molecules disclosed by the Wheeler *et al.* publication do not exhibit this property. *See, e.g.*, Wheeler *et al.*, Fig. 8. Use of the compounds disclosed by the Wheeler *et al.* publication as a mixture would render the mixture unsatisfactory for the purposes intended by the Sounik *et al.* publication, as light absorption would not occur over the desired range of wavelengths. Thus, no motivation for the asserted combination of references can be found in any common light absorption characteristics shared by the Wheeler *et al.* and Sounik *et al.* publications. *See, e.g.*, MPEP 2143.01 (the proposed modification cannot render the prior art unsatisfactory for its intended purpose).

There is no suggestion of similar uses in the cited publications

Furthermore, there is nothing in either publication cited by the Examiner indicating that the molecules disclosed in the primary Sounik *et al.* publication have similar uses to those disclosed in the secondary Wheeler *et al.* publication. The objects of the Sounik *et al.* publication are to provide a mixture of tetrazaporphin dyes which exhibits light absorption over a spectrum range of about 660-850 nm; a thin film optical recording medium; an optical light switch; and a light modulator device. *See, e.g.*, Sounik *et al.*, page 2, lines 43-44; page 4, lines 3-4; and page 4, lines 31-32. The characteristics of useful dye mixtures include an external field-induced noncentrosymmetric molecular orientation; second order nonlinear optical susceptibility; third

order nonlinear optical susceptibility; and bistable states of light transmission. *See, e.g.*, Sounik *et al.*, page 3, lines 10-11; and page 4, lines 27-32.

In contrast, the Wheeler *et al.* publication indicates that the molecules disclosed therein exhibit electrogenerated chemiluminescence (which is unrelated to any of the properties disclosed in the Sounik *et al.* publication) and do not provide light absorption over a spectrum range of about 660-850 nm. The Wheeler *et al.* publication is also silent as to external field-induced noncentrosymmetric molecular orientation; second order nonlinear optical susceptibility; third order nonlinear optical susceptibility; and bistable states of light transmission with regard to the molecules disclosed therein. Thus, motivation for the asserted combination of references cannot be found in any common uses shared by the Wheeler *et al.* and Sounik *et al.* publications.

The rejection is based on hindsight

Applicants respectfully submit that, when the cited publications are properly considered, it is apparent that any motivation to modify or combine the cited publications in order to provide the instant claims can only be gleaned in hindsight using the instant specification as a guide. Thus, in the absence of the teachings of the instant application, the skilled artisan would not have a motivation to combine the publications as the Examiner contends. Because a motivation to modify the cited art must be found in the prior art, and not in applicant's own disclosure, no *prima facie* case of obviousness has been established. *See, e.g., In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2142.

The claimed compounds unexpectedly exhibit fluorescence energy transfer and reduced quenching when used in particles

Applicants also respectfully submit that the claimed fluorescent particles exhibit unexpected properties that overcome any *prima facie* case of obviousness that may have been established by the Examiner. Specifically, when the dye pairs are included in a single particle, fluorescence energy transfer ("FET") occurs between the members of the dye pair. In FET, all or a portion of the energy absorbed by one member of a dye pair (the "donor") is not emitted as detectable emission light by that member; instead, the energy is "transferred" to the second member of the dye pair (the "acceptor") and emitted at the longer emission wavelength of the

acceptor. As described in the instant specification on page 40, lines 10-19, FET was confirmed in the particles of the instant invention by liberation of the dyes and measuring the loss in emission intensity of the acceptor dye. The FET parameters of the particles of the present invention are described in detail in the Example beginning on page 43, line 21.

The possibility that such molecules might exhibit FET when provided in a particle is not disclosed or even suggested by any publications of record. This property provides advantages in certain assays, as the Stokes shift exhibited by the fluorescent particle may be "tuned" to provide light absorption outside wavelengths absorbed by the sample of interest or detected as background by the fluorescence detector, and light emission at a wavelength that avoids losses in intensity necessitated by the use of filters in the detection optical path. *See, e.g.*, specification, page 2, lines 13-29, and Example 64, beginning on page 84.

In addition, as described in the instant specification on page 87, incorporation of tetraazaporphyrin dyes in particles can result in dramatic quenching of the fluorescence signal. The use of axial ligands such as bis(dimethylhexylvinylsiloxide) can dramatically reduce this quenching. Again, this unanticipated property is not disclosed or even suggested by any publications of record.

Because no *prima facie* case of obviousness has been established by the Examiner, or, in the alternative, because any *prima facie* case of obviousness has been rebutted by a showing of unanticipated properties of the claimed invention, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103.

Applicants also respectfully traverse the rejection of claims 31 and 45 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Sounik *et al.* and Wheeler *et al., J. Am. Chem. Soc.* 106: 7404-10 (1984) in further view of Vener *et al., Anal. Biochem.* 198: 308-311 (1991). Applicants submit that the Examiner has not established a motivation to combine the publications as suggested by the Examiner.

The Sounik *et al.* and Wheeler *et al.* publications are discussed in detail above. The Vener *et al.* publication is cited solely for its disclosure of latex particles of 1.8 μm in diameter for use in hybridization assays. The Examiner contends that the skilled artisan would allegedly be motivated to use the "dyes" disclosed by the Sounik *et al.* and Wheeler *et al.* publications in latex particles because "Sounik *et al* and Wheeler *et al* teach that these dyes are highly water soluble, stable and possess favorable fluorescent properties." Paper No. 9, page 14. Applicants respectfully disagree.

Nothing in the Sounik *et al.* and Wheeler *et al.* publications indicate that the molecules disclosed therein are "highly water soluble" as the Examiner contends. Indeed, given the extremely hydrophobic character of such molecules, the skilled artisan would read the cited publications as indicating that such molecules are insoluble in water. *See, e.g.*, Sounik *et al.*, page 7, lines 1-2 (the solvent will ordinarily be an organic solvent); Wheeler *et al.*, page 7405, right column 8th paragraph (the compound is soluble in organic solvents). Applicants respectfully request that the Examiner cite some supporting evidence for the water solubility properties to which the Examiner refers. Moreover, nothing of record indicates any relationship between "water solubility" and the use of dyes in latex particles. Thus, even if it is true that the "dyes" disclosed by the Sounik *et al.* and Wheeler *et al.* publications are water soluble, this fact by itself is not a motivation for the suggested combination of publications.

Furthermore, the Examiner indicates that the Sounik *et al.* and Wheeler *et al.* publications "teach that these dyes are... stable and possess favourable fluorescent properties." Paper No. 9, page 12. Again, the cited publications show no such thing. Rather, Applicants respectfully submit that this statement takes out of context the equivocal general statement in the first line of the Wheeler *et al.* publication.

Additionally, the Examiner is incorrect that Sounik *et al* and Wheeler *et al* teaches [sic] that their 'phthalocyanine dyes' can be combined with polymers such that would be used to make latex (see Sounik et al, page 2, lines 48-51)." Applicants respectfully submit that the cited passage of the Sounik *et al.* publication is unrelated to latex. The skilled artisan would readily acknowledge that "latex" is a colloidal dispersion of small (*e.g.*, submicroscopic) particles. In contrast, the cited passage of the Sounik *et al.* publication refers to manufacture of dye/polymer

blends by melting and molding. Applicants respectfully request that the Examiner cite some supporting evidence for the use of the materials referred to in the cited publication for the formation of latex particles.

As discussed above, no motivation has been established to combine the Sounik *et al.* and Wheeler *et al.* publications as suggested by the Examiner. The Vener *et al.* publication does not correct the flaws in the *prima facie* case of obviousness, nor is it suggested that it does so by the Examiner. Because no *prima facie* case of obviousness has been established by the Examiner, or, in the alternative, because any *prima facie* case of obviousness has been rebutted by a showing of unanticipated properties of the claimed invention, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103.

Obviousness-type double patenting

Applicants acknowledge the obviousness-type double patenting rejection of claims 30-31, 42, and 45. Should the claims be found allowable as presently written, a terminal disclaimer will be submitted.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

Date June 16, 2003

By _____

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